Seibert (A.)

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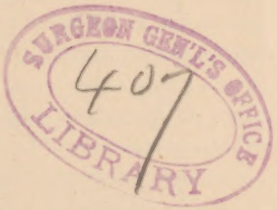

A SUBMEMBRANOUS LOCAL TREATMENT OF PHARYNGEAL DIPHTHERIA.

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Primarily the diphtheric process is a local disease. It is caused by the invasion of bacteria into the mucous membrane of the respiratory tract, which produces an inflammation of the invaded region. It is now conceded by most bacteriologists that in the majority of cases of diphtheria the bacillus found by Klebs and Loeffler is the chief cause of this disturbance. Inoculations of cultures of this bacillus upon guinea-pigs and rabbits, as well as bacteriological research by clinicians like Heubner, leave little doubt in this direction.

Yet other pathogenic germs besides this one may enter the mucous membrane in company with the Loeffler bacillus in a large proportion of cases, thus causing clinical pictures varying as to the aspect of the membrane produced, as well as to the extent, more or less pernicious character, and duration of the diphtheric invasion. If from a purely practical standpoint one might venture to suggest an idea not exclusively belonging to clinical experience, I should say that to my mind these varying pictures of the diphtheritic pro-

cess in different cases (though often observed in the same epidemics, at the same time, and in members of the same families) were caused by the *different proportions* of these different kinds of bacteria, entering the mucosa at the same time, so that where other pathogenic germs than the true diphtheria bacillus of Loeffler were in the majority, this most pernicious micro-organism did not find the surroundings favorable enough for a full development of its growth, and was curtailed in its action on the human tissue by this fight for place, so as to only result in more or less milder forms of diphtheria. At all events, we at the present time, mindful of the works of Oertel, Brieger and Fraenkel, and others, may logically assume that the more bacilli of Loeffler are found in a given case of diphtheria, the more fatal its prognosis, and the smaller the quantity of these germs in a case, the milder its form.

Roux and Yersin have again called attention to a pseudo-bacillus of diphtheria, having no virulence, but otherwise very much like the true germ, which appears to become virulent when associated with Fehleisen's coccus of erysipelas. If this can be so, then other bacteria may have the power to decrease the virulence of others.

The changes brought about in the tissues of mucous membranes by the invasion of the bacteria causing diphtheria have been elaborately demonstrated by Oertel in his great atlas. The histology of the pseudo-membrane proper has found a most careful student and explicit demonstrator in Heubner. He has examined the pseudo-membrane in cases from five hours to six days old, and his results have thrown considerable light on the diphtheritic process. In a drawing from Heubner's work, showing the normal conditions of the epithelial layers of the tonsillar mucosa of a child (Fig. 1), we find the upper layer to consist of flat, horny, the middle of round, and the lower

stratum of oval-shaped epithelial cells, below which last we notice large round cells, connective tissue, and blood-vessels. Heubner found that even the first noticeable trace of the diphtheritic pseudo-membrane (taken from the tonsil five hours after the beginning of the attack) consisted of an ex-

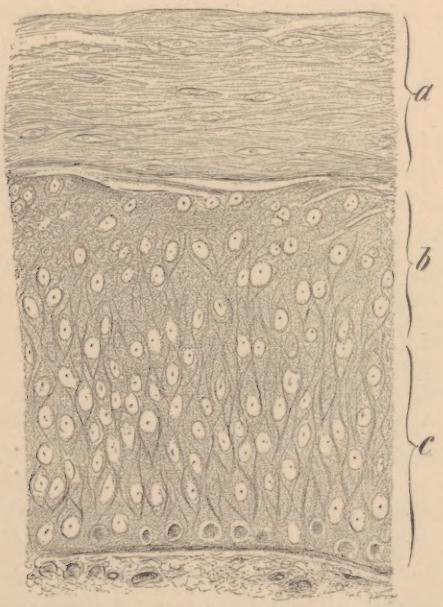

FIG. 1.—*a*, upper epithelial layer; *b*, middle epithelial layer; *c*, lower epithelial layer; below, the connective-tissue layer of the mucosa.

udate coming from *the inflamed blood-vessels*, which after wandering upward with the numerous leucocytes (white blood-corpuscles) between the oval and round cells of the epithelium, lodged between the horny upper cells and there coagulates, imbedding within it numerous bacteria. This stream of exuding fibrin, from below upward, keeps on

steadily as long as the action of the bacteria upon the blood-vessels and their surrounding tissue progresses, ultimately resulting in all the epithelial layers being permeated, distended, and infiltrated by this coagulated fibrin, so that (as Heubner has it) while in the beginning of a case the exudate is imbedded between the epithelium, in advanced cases the epithelium (or what is left of it) is imbedded in the exudate (Fig. 2, taken from Ziegler's *Pathological Anatomy*).

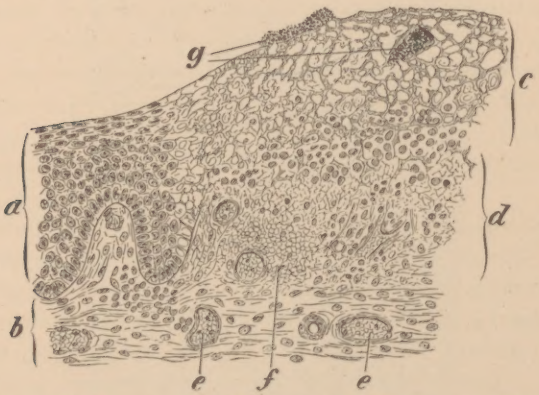

FIG. 2.—*a*, epithelium; *b*, connective-tissue layer of the mucosa; *c*, false membrane; *d*, infiltrated lower epithelium; *e*, blood-vessels; *f*, extravasated blood.

The practical lesson we may learn from these facts is that the appearance of the pseudo-membrane is the sure sign of bacterial action upon the *lower* layers of the mucosa, directly below this sign of this invasion.

All investigators unite in stating that far more bacteria are found in the epithelium and the pseudo-membrane than in the tissue below. No doubt many of the active bacteria are carried away by the circulation after penetrating the blood-vessels, and others are carried upward with the flow-

ing exudate, to be imbedded in the coagulated mass at the periphera.

L. Brieger and C. Fraenkel have lately demonstrated the chemical body produced by the action of the Klebs-Loeffler bacillus upon the albumin of the pseudo membrane, which getting into the circulation produces the different varieties of diphtheric paralysis. This ptomaine, called by these authors "toxalbumin" of diphtheria, is produced in but small quantities in the early stages of each case, but the larger and older the diphtheric area, the more toxalbumin is produced. Injected into the circulation of animals, this toxalbumin invariably produces paralysis.

The conclusions as to the treatment of diphtheric patients we may logically draw from these facts are:

1. The pseudo-membrane is an exudate coagulated in the epithelium coming from the deeper layer of the mucous membrane, and therefore not the disease, but the result of it.

2. Hence all treatment attempting to dissolve or to forcibly take away this pseudo-membrane *is to no purpose*, as it does not in the least affect the diphtherically inflamed parts.

3. All medicines given by the mouth for the purpose of entering the invaded region of the mucosa are of no use whatsoever in this direction, as they can not possibly penetrate the coagulated fibrin and swollen epithelium to reach the bacteria producing this affection.

4. All local applications of strong caustics—as the galvano cautery, nitrate of silver, etc.—are of no avail, as the diphtheric germs are far beneath the reach of these agents (Fig. 3, action of nitrate of silver upon diphtheric mucosa. Oertel, Plate No. XVI).

Tests of Loeffler and others have shown that the bacteria causing diphtheria can not be destroyed at all by weak

antiseptic solutions. The bichloride of mercury, for instance, given internally, dissolved in 10,000 parts of water, could not destroy this bacillus even if it were completely surrounded

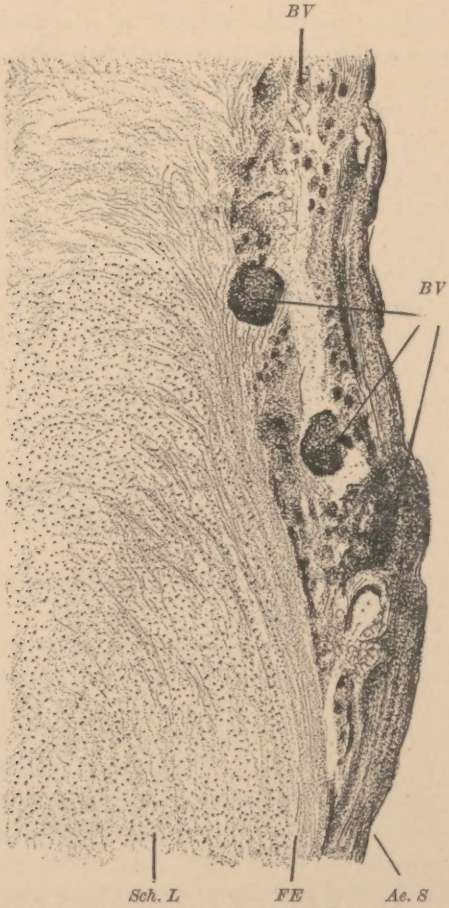

FIG. 3.—*Ae. S*, eschar from nitrate of silver; *FE*, *Sch. L*, infiltrated mucosa; *BV*, bacteria.

by it. Given as it is in teaspoonful doses by the mouth, it passes gently over the pseudo-membrane into the stomach of the patient, from there into the circulation, and the little of it that may come in contact with the bacilli in the diseased mucous membrane can possibly be of no account in even retarding their action. As this remedy is one of the strongest antiseptics known to act upon bacterial life and in particular upon the Loeffler bacillus, it at once appears superfluous to speak of the legion of other drugs which for decades back have been proposed for the treatment of this dreadful disease.

So we can but admit that the methods so far employed in attempting to aid the human organism in resisting this bacterial poison and its products have accomplished but little, if anything at all, *because the remedies we were compelled to use are too weak and because they do not reach the seat of this pathological process.* After coming to this conclusion and throwing aside all superfluous clamor, it behooves us to now attempt to remedy these faults of treatment.

The first imperative necessity brought before us, then, must be to bring whatever remedy we have in direct contact with those bacilli which are in full action upon the tissues. As we can not possibly use the knife and cut down upon the lower stratum of the mucous lining of the tonsils and the pharynx, we must devise other means to bring our drug to the right spot.

For this purpose I have devised an instrument, consisting of three parts: (1) A hypodermic syringe, (2) a tube strong and long enough to reach the pharynx, and (3) a small hollow plate which can be screwed on the end of this tube, holding the points of five hollow needles. When screwed together, these three parts form a firm, handy, and pliable instrument that may easily be introduced over

a child's tongue, pressing it down, the points of the needles pointing upward into the pharynx.

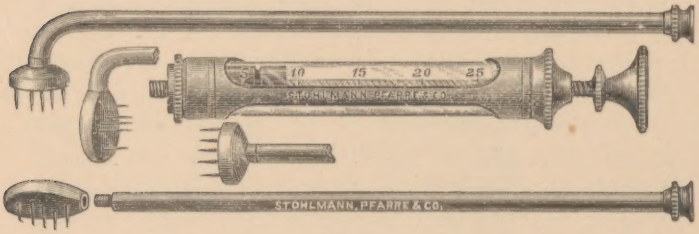

Fig. 4.

Supposing we had a fresh case of diphtheria, and a pseudo-membrane of the size of a pea on the side of the right tonsil. The needles, the tube, and a part of the syringe being filled with an antiseptic fluid, the instrument is passed over the tongue to the tonsils, the returned toward the pseudo-membrane, and, by a quick and gentle pressure, the needles are plunged through the pseudo-membrane and some of the mucosa surrounding it. Now, while three fingers of the left hand hold the instrument in this position, the fluid is gently pressed out of the syringe proper and *into and below the inflamed mucosa beneath the pseudo-membrane.* The plate only permits of the needles passing into the tissues to the depth of an eighth of an inch, all told. The needles are then withdrawn, and the remedy is in contact with the seat of the disease.

Five points are used, as I have thought it wise to deposit five distinct little masses of remedial fluid, because the latter would thus cause less inconvenience by pressure, would cover a greater area, and be more readily distributed in the neighborhood. If gently performed, this little operation causes no pain, at least not in adults and children that are sensible enough to speak for themselves. The fluid re-

mains in the tissue, and, as a rule, not a drop of blood is lost.

The curved catheter-shaped tube may be attached to either one of the two plates, so that by the four different combinations any part of the visible pharynx, and even the rear surface of a large tonsil, may be reached.

Intratonsillar injections with a single hypodermic needle have been employed by Heubner in the treatment of scarlatinous amygdalitis for the last eight years, and but lately he has again recommended their use (with a three-per-cent. solution of carbolic acid), yet he does not employ them in primary diphtheria, knowing well that a single injection into the depth of a tonsil would not reach the disease, would be quickly absorbed, and could not be employed in the other parts of the pharynx. But lately, in speaking of diphtheria, he discards all active treatment.

It appears to me of the greatest importance to bring the drug directly *into and below* the diseased part, and to introduce the needles *through and around* the pseudo-membrane. The active bacilli in the *lower* stratum of the mucosa will thus be reached, the tissues there thus made uninhabitable to further possible invasions from above, the exudation must cease, and the whole process come to a stand-still. The pseudo membrane, on the other hand, is the *only true guide* to the diphtheric inflammation below it.

After having convinced myself (by practical tests on numerous patients suffering from various throat affections) of the pliability of this diphtheria syringe, I naturally looked about for a remedy for injection. Carbolic acid in a three-per-cent. solution had a good effect on a few cases of tonsillar diphtheria—cases that might possibly have ended as favorably under the use of chlorate of potassium or salt water. To really have a germicidal action, it appeared to me to be essential to use a *very strong* antiseptic—one that would im-

mediately destroy the vitality of the Loeffler bacillus. Here a strong solution of the bichloride of mercury suggested itself, but so far I have been too timid to make use of it. Aniline had lately been mentioned as a non-poisonous antiseptic, and encouraged by Dr. von der Goltz, of this city, who had used the pure aniline in a solution of 1 to 1,000 in a large number of gynæcological and obstetrical cases as an antiseptic wash, apparently with marked success, I concluded to make some experiments to first test its possible poisonous action on the animal system and then its possible antiseptic properties. Assisted by Dr. von der Goltz, I injected four grammes (one drachm) of a ten-per-cent. alcoholic solution of aniline under the skin of a cat, above the gluteal muscles. Thirty minutes after this injection the animal ate a hearty supper, and, after having shown not the slightest sign of poisoning (no change of heart action or respiration in particular), it was killed rapidly by a large dose of chloroform. On section, I found that the aniline had permeated all tissues surrounding the point of injection to the extent of about three inches, and in particular the muscles. A piece of muscle was then put into a large test-tube, and about a teaspoonful of my own saliva added to it. As bacteria are always present in the oral cavity and as I had no cause to think that they were of a particularly virulent type, I argued that, if at all antiseptic, the large quantity of aniline in this muscle would prevent any noticeable bacterial action for some time at least. After forty-eight hours this muscle, soaked full with aniline, was in a high state of decomposition, giving a most offensive smell and showing grayish discoloration on its surface. This simple test was sufficient for me to discard aniline as an antiseptic.

J. Geppert (Bonn), in a series of painstaking experiments, tested some of the stronger antiseptics now in use as to their action upon the anthrax bacillus. I can here

but briefly mention his results, showing that this bacillus will live for days in a 7-per-cent. solution of carbolic acid; if hanging in the fibers of a silk thread dipped into a solution of the bichloride of mercury of 1 to 1,000, will live and thrive if removed after twenty minutes; and if spread on a cover-glass and dipped into the same solution, will breed cultures if removed after five minutes. The next tests were made with chlorine water (aqua chlori) of a 0·2-per-cent. solution and of a 0·15-per-cent. solution, which all resulted in showing that the anthrax bacillus was destroyed in ten seconds if brought in contact with this antiseptic, while a 1-to-1,000 solution of the sublimate could not do the same work in fifty seconds. Geppert furthermore showed that that antiseptic was most powerful which was capable of penetrating those media containing the micro-organisms. This also was found to be chlorine. Moist strata are permeated more readily than dry ones. The disinfecting action is a chemical one.

Instigated by these important tests of Geppert's, I resolved to try the action of chlorine water upon the diphtheritic process. Three points had to be considered: (1) if it was safe to inject a 0·2 per cent. solution of aqua chlori into the tissues without poisonous effect; (2) to determine the local irritation and readiness of absorption if injected; (3) to see if chlorine water would penetrate coagulated blood-albumin and tissue, like epithelial cells and leucocytes.

To determine the safety of hypodermic injections of chlorine water, I injected half a gramme of a 0·2-per-cent. solution of it under the mucous membrane lining the mouth of a white rabbit weighing four pounds and a half. Another rabbit of the same age and weight was kept for comparison. No poisonous symptoms appeared. Even a whole syringeful of this solution, injected hypodermically in the gluteal

region, did not impair the animal's health in the least. The injections below the mucosa of the upper lip plainly showed a hard zone for days, evidently due to coagulation of albumin caused by the chlorine after the water had been absorbed. From these experiments I concluded that (1) it was perfectly safe to inject this chlorine water into the mucosa of a child, and (2) that the local irritation caused was not of any account, and that the chlorine evidently immediately went into chemical combinations with the surrounding tissues and was but slowly absorbed. To see if chlorine water would penetrate coagulated blood albumin, Mr. Otto Amend was kind enough to experiment. His answer was an affirmative one. To see if epithelial cells and blood-corpuscles were acted upon, I took a drachm of urine of a patient suffering from pyelitis and purulent catarrh of the bladder, divided the portion in two equal halves in two test-tubes, and added five drops of the chlorine water to the one. After shaking, I took a drop of this mixture and placed it under the microscope. Another drop was taken from the other tube, containing the unmixed urine, upon another slide. Upon comparison, we find that the drop containing urine with chlorine water shows the white blood-corpuscles and epithelial cells acted upon in such a way that their borders look heavy, thickened, and somewhat irregular, the nuclei and nucleoli dark and irregular, and corpuscles as well as epithelium look as though their pictures had been first drawn by pencil and then overdrawn by ink. The constituents of the non-chlorated urine show clear, transparent, and light pictures. (Fig. 5.)

Repeated experiments always gave the same result. Evidently the dark, heavy spots and borders of corpuscles and epithelium were the work of the chlorine and the result of a chemical change caused by the contact of this drug with the albumin of these tissues. I deduced from this

that if chlorine would even penetrate the epithelial cells and the white blood-corpuscles, it certainly would invade every particle of mucous tissue it came in contact with.

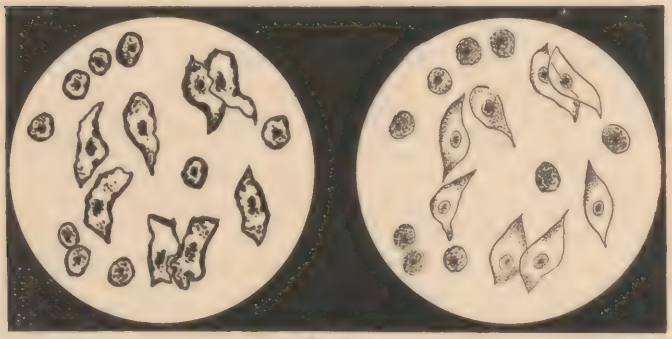

FIG. 5.

I now made chlorine-water injections into the hypertrophied tonsils of adults. Two large drops, divided into five equal proportions by the five needle-points, were injected at one time. The inconvenience caused was hardly noticeable. A sense of pressure appeared, which left the patient after a few minutes. The introduction of the needle-points was hardly felt by the patients.

Being now prepared to use this method and this drug, I made two injections into the tonsillar mucosa of a child of three years, two drops of the 0·2-per-cent. solution being used in each tonsil. This little girl was suffering from a fresh attack of diphtheria of three days' standing, both tonsils showing well-marked pseudo-membranes of doubtless diphtheric character. Glands of neighborhood infiltrated; temperature, 103° F. Sister of child had died of diphtheria a few months before. Injection at 5.30 P. M. Temperature at 9 P. M. down to 101°, and 99° F. next morning. The surrounding parts were now pale, while at time of injection the whole pharynx seemed very red

and œdematous. Pseudo-membranes drop off in two days. Appetite of child appeared four hours after injection.

In my second case (a boy, aged two years and three quarters, whose sister had died of malignant diphtheria ten days before) I found diphtheric inflammations on both tonsils, which were in a state of enormous chronic hypertrophy. The right tonsil presented a fresh pseudo-membrane, while the left showed a spot of about a quarter of an inch in diameter, looking as though a drop of milk had fallen on it and spread, the very first sign of a pseudo-membrane. Temperature, 101·75° F.; infiltration of glands; vomiting. Injections, 10 A. M. At 4 P. M. temperature normal; appetite. Pseudo-membrane dropped off within thirty-six hours.

Cases III, IV, and V were very much like this one, all three patients being relatives of Case II.

Case VI.—Boy of four years. Visited a family where a child had been sick with diphtheria three months before. Boy was given toys of this child, especially a trumpet, which had been used by the diphtheric child during its illness. Forty-eight hours after this visit symptoms began. I did not see the child until four days after the visit. Diagnosis: Diphtheria of both tonsils and sides of pharynx, stenosis of larynx, trachea, and larger bronchi, due to diphtheric invasion. Injections of chlorine water through both pseudo-membranous patches in pharynx. Twelve hours later pharynx pale, no extension of pharyngeal diphtheria, the œdema of soft palate subsided; stenosis worse. I now intubated the larynx, bringing but partial relief, as disease had previously extended far below the reach of the O'Dwyer tube. Two days later the child died of paralysis of the heart, but the day before the pseudo-membrane of the pharynx had disappeared entirely. Though in private practice, the parents gave their consent to a post-mortem, which showed an exquisite extension of the diphtheric process all along the bronchi of the first and second order, with formation of pseudo-membrane. The specimen was demonstrated to my class at the New York Polyclinic immediately after the autopsy.

Case VII, the last I shall report, concerned the nine-year-old brother of the little girl in Case II. Illness began suddenly

with severe headache and vomiting. Twenty-four hours later I found a dark, slate-colored pseudo-membrane about half an inch in diameter on both tonsils. The whole pharynx œdematous, very red; the uvula much enlarged. Swallowing very difficult. Glands swollen. Temperature, 102·75° F. It needed the assistance of the O'Dwyer-Denhard gag and of three men to overcome the struggling of the boy to succeed in making the first submembranous injection. The second one could be made easily, as the patient lost all fear after the first one, and stated: "If that's all, you can do it again." At the next visit the throat was pale, the swelling reduced markedly, the temperature 100·25° F., the feeling of illness entirely gone, and boy asking for beefsteak. The pallor of the mucosa surrounding the pseudo membrane was as distinct in this case as in all others. The œdema of the uvula and soft palate had diminished considerably. The next day the general improvement persisted, the left tonsil losing its pseudo-membrane till evening, that of the right growing smaller to one half of its extent. But, as the temperature showed a rise again to 101·5° F., I looked for and found a new diphtheric patch on the side wall of the pharynx back of the right tonsil. I concluded to make another injection at this point, which now was done without the slightest resistance from the boy and without the aid of spoon or gag. Next day both tonsils were clean, temperature was normal, and the pea-like pseudo-membrane disappeared by evening.

These seven cases (from private practice) demonstrate fully—

1. That this method of treatment can be employed without inconvenience and danger to children.

2. That the chlorine water, thus brought in contact with the Loeffler bacilli and the inflamed parts, evidently tends to check their career in the mucous membrane and to shorten the disease.

3. That it seems worth while to give this method a full trial.

One word more about the handling of the apparatus:

The chlorine water must be kept cold and dark, and is best carried constantly with the instruments in an outside overcoat pocket. This will insure purity and correct strength of the solution and, before all, will avoid delay, for the sooner the injection is made the better the prognosis of the case. I do not expect to influence cases by this method where the diphtheric inflammation has spread over the half or whole of the oral cavity, and I hardly think that I would make any attempts at using it, but I have good cause to think that we may prevent such spreading by these injections almost with certainty if employed in time.

The needles and the whole instrument are easily disinfected by the same chlorine water and soap and water externally; the inner surface, never coming in contact with diphtheria, is nevertheless disinfected by the chlorine.

The needle-points must be wired carefully and the whole syringe cleared of the chlorine water thoroughly. Of course some corroding will come in time, and a new needle-plate will now and then be necessary; but what is that in comparison to what we may accomplish with it?

Whether the chlorine water will remain the best chemical to use or not, I am not prepared to say. Other remedies may also be used with effect.

In speaking of future methods of treatment in an article published last February I said: "If we now vaccinate organisms into the circulation of healthy persons to prevent disease, why may we not come to impregnating microorganisms into those already diseased?" And so I hope to see the day when Koch or one of his pupils will give us a lymph that we may inject into diphtheric tissues. By that time my little instrument may be so improved that it will fully answer this purpose also, yet till then even, I am convinced, it will help to save children from an early grave if employed in time.

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